Exhibit 6

Antidepressants in Long-Term Migraine Prevention

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Abstract

Migraine and depression coincide in some 20–30% of patients. Although antidepressants (namely tricyclics) are not considered as first-line prophylactic compounds in patients with migraine alone, several clinical trials support a remarkable benefit in the treatment of migraine and related headache disorders. However, treatment with one antidepressant alone often does not suffice to treat both disorders effectively. Therefore, combinations of classical antidepressants with both newer antidepressants and established prophylactic drugs (e.g. β-adrenergic receptor antagonists [β-blockers], topiramate and sodium valproate) are required. In addition, acute attack medication (such as triptans, ergotamines or analgesics) is regularly combined with the preventive medication, thus requiring elaborate knowledge about the complex network of potential interactions and contraindications. Fear of potentially serious interactions can frequently lead to insufficient treatment of both underlying disorders, with an enormous impact on the patient's life. Pathophysiologically, multiple neurotransmitters have been attributed an important role in the aetiology of migraine (mainly serotonin and calcitonin gene-related peptide) and depression (among others, serotonin, dopamine and noradrenaline [norepinephrine]). Most drugs used to treat both disorders influence at least one of these transmitter systems, such as classical tricyclics. This review discusses the efficacy of antidepressants in migraine prevention. In addition, recommended combinations in patients with concomitant depression and migraine are presented with regard to their proposed pharmacological mechanism of action and their potential interactions.

Migraine is an episodic headache disorder characterized by recurrent attacks of severe and mostly unilateral undulating pain, typically accompanied by nausea and vomiting as well as photo- and phonophobia.[1] The current diagnostic criteria are listed in table I. Regular concomitant complaints are photophobia, phonophobia, osmophobia, vertigo, nausea and vomiting.[2] Various forms of preceding transient neurological deficits and positive symptoms, the so-called 'aura', are found in 15–20% of the patients, the most frequent being a visual aura in approximately 90% of all migraine patients with aura.[3] The prevalence of migraine is 6–8% for men and

Table I. Diagnostic criteria of migraine according to the International Headache Classification Committee[1]

Migraine without aura (IHS 1.1)
A. At least five attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
1. Unilateral location
2. Pulsating quality
3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
1. Nausea and/or vomiting
2. Photophobia and phonophobia
E. Not attributed to another disorder

12–14% for women, but also approximately 5% of children experience migraine. The peak incidence of migraine attacks occurs in those aged 35–45 years.[4,5]

Migraine is associated with various diseases such as patent foramen ovale,[6] lower systolic blood pressure[7] and fibromyalgia.[8] Over 40 years ago, Wolff[9] mentioned an association between migraine and depression, as did Selby and Lance.[10] Kashiwagi[11] and Couch et al.[12] substantiated these observations by showing an increased incidence of depression in migraineurs. Couch and Hassanein[13] showed that migraine and depression responded independently to amitriptyline, rejecting theories migraine was caused by depression. Today, apart from depression,[14-16] bipolar disorder and anxiety disorders (particularly panic disorders) are associated with migraine.[17,18] These results have been confirmed by a large American population-based study.[19] The HUNT study (Nord-Trøndelag Health Study)[20] confirmed a stronger association between migraine with aura and depression alone or depression with a co-morbid anxiety disorder than in patients without aura. However, this effect was only verified for females.[20] Recently, a bidirectional influence of migraine and depression on each other was identified. In patients with severe depression, the risk of developing migraine was significantly higher than in non-headache individuals and vice versa.[21] In a subgroup of women with migraine, those with depression and anxiety had the highest disability and lowest quality of life scores compared with other non-psychiatric co-morbidities.[22] In clinical practice, this co-morbidity can complicate the treatment in either disease and requires the use of antidepressants.[23] In this review, we discuss the role of antidepressants in the prevention of migraine attacks, their important interactions and adverse effects.

We searched MEDLINE for literature with the keywords 'antidepressant' and 'migraine', 'antidepressant' and 'headache', and the individual drugs presented in the article in combination with 'migraine'. The last search was performed on 5 September 2008. Only articles published in English or German were considered. Articles located were reviewed, as well as the referenced studies cited therein. In addition, review books in English and German were considered.

1. Pathophysiology of Migraine

Migraine is regarded as a complex neurological disorder (and not a vascular disease) with environmental, genetic, neuroanatomical, neuroimmunological, neurochemical and neurophysiological aspects.[24,25] Unlike former theories, vascular changes have clearly been identified as secondary phenomena. Cortical spreading depression has been suggested to be the initiating mechanism of migraine with aura.[26]

Another cornerstone in migraine pathophysiology is the sensitization of perivascular trigeminal sensory nerve endings in the meninges, which coincides with a neurogenic inflammation with plasma protein extravasation. The neuropeptide calcitonin gene-related peptide (CGRP) is produced in trigeminal ganglion neurons and exerts vasodilatory effects, stimulates the production of inflammatory cytokines and nitric oxide, and enhances transmission of nociceptive input to the CNS.[27] Not surprisingly, elevated CGRP levels in blood from the external jugular vein were found, which decreased after effective abortive therapy.[28] Administration of CGRP antagonists such as olcegepant[29,30] or

telcagepant showed promising results in acute migraine attacks in humans.[31] Recently, another CGRP receptor antagonist (BMS-694153) with rapid intranasal absorption has been presented.[32] Secondary to this peripheral sensitization, a secondary sensitization of pain pathways, mainly the trigeminothalamic tract, was suggested by Burstein et al.[33] who showed a facilitation during a migraine attack with the phenomenon of 'cutaneous allodynia'.

Historically, serotonin has played an important role in pathophysiology of migraine,[34,35] as the currently most important family of drugs in clinical practice, the triptans, are serotonin receptor agonists (see table II). Sicuteri et al.[39,40] discovered an altered serotonin metabolism in acute migraine attacks more than 40 years ago. Serotonin levels are lowered in platelets and in plasma during a migraine attack, while an increase in the excretion of serotonin and its metabolite 5-hydroxy-indolacetic acid can be observed.[41] Additional drugs with some effect in migraine were identified, which target different serotonin receptors, for instance the serotonin 5-HT_2-receptor antagonist methysergide (a synthetic ergotamine derivative). Other drugs modulating serotonin metabolism with efficacy in migraine, such as the non-selective serotonin and noradrenaline (norepinephrine) reuptake inhibitor (SNRI) amitriptyline, support the significant role of serotonin metabolism in migraine pathophysiology.[41]

However, there is more to migraine than serotonin alone, as shown by the impressive results with CGRP antagonists. It has been hypothesized that migraine is a central neurochemical imbalance with a predisposition to low serotonin levels, which could facilitate nociceptive trigeminovascular pathways.[42] The importance of serotonin in migraine and its unquestionable role in the pathophysiology of depression is intriguing. However, depression has been attributed not only to a depletion of serotonin, but other neurotransmitters such as dopamine and noradrenaline. Interestingly, those antidepressants influencing more than one neurotransmitter (e.g. amitriptyline and venlafaxine) have shown the best efficacy in migraine therapy, so that perhaps a complex neurochemical imbalance has to be targeted by beneficial drugs.

2. Use of Antidepressants as Prophylactics

The clinically relevant classes of antidepressants and their predominant modes of action are given in table III.

2.1 Nonselective Reuptake Inhibitors

2.1.1 Amitriptyline

Amitriptyline is the most widely used prophylactic tricyclic antidepressant. The agent inhibits both noradrenaline and serotonin reuptake and exerts some $5HT_2$-receptor antagonistic effects.[45] The efficacy of amitriptyline to treat headache disorders dates back to 1964, when Lance and Curran[46] found it to be useful in tension-type headache. Later, placebo-controlled

Table II. Relevant pharmacological effects of serotonin (5-HT) receptor agonists[36-38]

Receptor subtype	Mechanism	Pharmacological effect
5-HT_{1A}	Inhibition of neuronal activity in the raphe nucleus	Anxiolytic, hypotension, sleep, thermoregulation
5-HT_{1B}	Presynaptic inhibition of serotonin release	Vasoconstriction (e.g. coronary arteries)
5-HT_{1D}	Inhibition of peptide release, presynaptic inhibition of noradrenaline release	Locomotion, cerebral vasoconstriction
5-HT_{2A}	Release of serotonin, neuronal excitation	Vasoconstriction/dilation, platelet activation
5-HT_{2B}	Nitric oxide release from endothelial contraction of gastric wall	Vasodilatation, neurogenic inflammation
5-HT_3	Depolarization of vagus associated afferent neurons, release of acetylcholine and cholecystokinin	Vomiting, nausea, anxiety
5-HT_4	Release of acetylcholine, atrial depolarization	Increased gut motility, positive inotropic and chronotropic effects

Table III. Classification of antidepressants[43,44]

Class of antidepressant	Examples of compounds
Nonselective reuptake inhibitors	Amitriptyline, imipramine, nortriptyline, clomipramine
Selective serotonin reuptake inhibitors	Citalopram, escitalopram, fluoxetine, sertraline, paroxetine
Selective serotonin noradrenaline reuptake inhibitors	Venlafaxine, milnacipran, nefazodone ($5\text{-}HT_2$-receptor-antagonist)
Selective noradrenaline reuptake inhibitors	Reboxetine, maprotiline
Noradrenergic and specific serotonergic antidepressants	Mirtazapine, mianserin ($5\text{-}HT_{2/3}$-receptor antagonists, increase release of serotonin, $5\text{-}HT_1$-receptor activation)
Monoamine oxidase inhibitors	Moclobemide, tranylcypromine, phenelzine

5-HT = serotonin.

studies in patients with migraine were performed,[13,46-48] as well as case-control and other studies,[4,49-53] with positive results (see table IV for further details of placebo-controlled studies).

Thus, amitriptyline is considered the antidepressant of choice for the prophylactic treatment of migraine. This tricyclic may be especially suited in patients with mixed headache syndromes (such as tension-type headache), in patients experiencing insomnia, and of course in those with concomitant depression. In paediatric migraine, amitriptyline showed a marked effect in an open-labelled study in 279 children (mean age 12 years), who showed a reduction in attack frequency of 50% after 2 months. Some 84% of the children stated a subjective improvement.[55] Lewis et al.[56] reported a reduction in the number of attacks per month by 62% in 73 children and adolescents in a retrospective analysis. However, the Cochrane review on preventative drugs in childhood migraine did not include amitriptyline, for methodological reasons.[57]

The dose of amitriptyline should be slowly increased, starting with 25 mg in adults (at bedtime) and increasing up to 75–100 mg, and up to 300 mg in hospital in case of concomitant depression. A decision with regard to efficacy is only realistic after several months of treatment. The most important adverse effects are drowsiness and anticholinergic symptoms such as dry mouth, constipation and tachycardia. Weight-gain occurs in many patients together with elevated levels of leptin, insulin and C peptide,[58] and can be a limiting factor leading to impaired compliance and discontinuation. Occasionally, amitriptyline may provoke an ileus or a delirium.[49,59,60] Glaucoma, PQ and QT interval prolongation on ECG, as well as benign prostate hypertrophy should be excluded prior to treatment. Although selective serotonin reuptake inhibitor (SSRI) for therapy of migraine and tension-type headache were significantly better tolerated than tricyclic antidepressants, the number of patients withdrawing as a result of adverse effects did not differ significantly in either group in a recent Cochrane review.[61] In case of intolerability, other tri- or tetracyclic agents such as doxepin or nortriptyline may be adequate alternatives.[62,63] Amitriptylinoxide is often said to be better tolerated, but shares a similar profile of adverse events.[64] Amitriptyline is metabolized by cytochrome P450 (CYP) isoenzymes, particularly CYP2D6, which is responsible for multiple interactions (see table V). Wong and colleagues[66] found an increase in plasma levels of amitriptyline and its active metabolite nortriptyline of some 42% after concomitant administration with sodium valproate and, therefore, proposed dose reduction of amitriptyline. On the other hand, fluoxetine or paroxetine, as potent inhibitors of CYP2D6, increase serum amitriptyline levels.

2.1.2 Clomipramine

Two placebo-controlled studies did not provide any evidence of efficacy in migraine prevention. Langohr and co-workers[67] compared clomipramine (up to 100 mg/day), metoprolol (up to 100 mg/day) and placebo in a double-blind, crossover design (n = 36). While intake of metoprolol resulted in a significant decrease of headache intensity and duration, beneficial effects of clomipramine were much lower and not significant. It is notable that the rate of adverse effects such as insomnia, sweating and tiredness in the clomipramine group was high (67%).

These negative results were confirmed by another placebo-controlled study,[68] which tested clomipramine in 21 patients in a randomized,

crossover fashion. Adverse effects were reported significantly more often in the verum group, while attack frequency decreased in both groups without a significant difference between them. However, methodological shortcomings (such as the absence of a run-in period, a low number of participants and a high withdrawal rate) limit the value of this study. Currently, there is no encouraging evidence for clomipramine in migraine prevention.

2.1.3 Doxepin

In a randomized, double-blind, crossover study, 23 patients experiencing a combination of migraine and tension-type headache received either doxepin 100 mg/day or placebo for 9 weeks, with a washout phase of 2 weeks. While the number of headache days per month did not decrease, a significant decrease in the consumption of concomitant medication was observed together with improved ratings on a proprietary headache index.[69] Patients receiving doxepin reported more adverse effects typical of tricyclics. However, the clinical significance of this study is decreased by the low number of patients, imprecise inclusion criteria, a combination of two primary headaches and a relatively high withdrawal rate. In summary, current data do not substantiate a relevant role of doxepin in migraine prevention.

2.1.4 Nortriptyline and Other Tricyclics

Nortriptyline predominantly inhibits noradrenaline reuptake and is a metabolite of amitriptyline. Although it is recommended in review articles,[63] there are currently no controlled studies supporting efficacy in migraine prevention. This also holds true for imipramine, trimipramine and desipramine. Positive effects are suggested for imipramine in single open studies ($n < 5$ patients receiving imipramine in each study).[56,70] Apart from amitriptyline, the remaining tricyclics (except for clomipramine) can be considered as second- or third-line alternatives in selected patients in the treatment of migraine and a concomitant depression, especially if a more activating or sedating effect is required compared with amitriptyline and if amitriptyline is not tolerated.

2.2 Selective Serotonin Reuptake Inhibitors

SSRIs currently used in migraine comprise citalopram, escitalopram, fluoxetine, fluvoxamine,

Table IV. Double-blind, randomized, placebo-controlled studies on amitriptyline (reproduced from Evers and Mylecharane[54] with permission)

Study (year)	N[a]	Design	Run-in	Drugs compared (daily dose)	Duration	Efficacy parameter	Result
Gomersall and Stuart[47] (1973)	26 (20)	co		Amitriptyline 10–60 mg, placebo	6 mo each	Frequency, duration migraine	Amitriptyline reduced frequency more than placebo
Couch and Hassanein[13] (1979)	162 (100)	pg	4 wk placebo	Amitriptyline 50–100 mg, placebo	2 mo	Migraine score, depression scores (Hamilton depression scale, Zung self-rating depression scale)	Amitriptyline reduced migraine score more than placebo, unrelated to depression
Ziegler et al.[48] (1987)	54 (30)	co	4 wk placebo	Amitriptyline 50–150 mg, propranolol 80–240 mg, placebo	10 wk (2 wk washout)	Headache score, depression scores (Hamilton depression scale, Zung self-rating depression scale)	Amitriptyline and propranolol reduced headache ache score more than placebo; unrelated to depression
Ziegler et al.[49] (1993)	30	co	4 wk placebo	Amitriptyline 40–150 mg, propranolol 25–240 mg, placebo	10 wk (2 wk washout)	Frequency, duration, severity, headache score	Amitriptyline reduced all parameters vs placebo; propranolol reduced severity and headache score more than placebo

a Number of patients included (number of patients evaluated).

co = crossover; **pg** = parallel group.

Table V. Amitriptyline is a substrate of cytochrome P450 (CYP) 2D6 and CYP2C19, which implies various interactions. Some important interactions are cross-tabulated with regard to clinical effect[43,65]

Effect	Increase of effect	Decrease of effect
Effect of amitriptyline	Fluvoxamine, fluoxetine, class Ia and IIIa antiarrhythmics, warfarin, opiates, prazosin, propranolol, diuretics, insulin, tolbutamide, phenytoin	Clonidine, guanethidine
Effect on amitriptyline	Fluvoxamine, fluoxetine, antipsychotics, cimetidine, quinidine, warfarin, valproate, propranolol, verapamil, omeprazole	Carbamazepine, opiates, cholestyramine, tobacco (nicotine), estrogens, rifampicin, barbiturates

paroxetine and sertraline. They selectively inhibit serotonergic reuptake, and have some antimuscarinic and antihistaminic potential. Several SSRIs have been tested in migraine prevention, with mixed results.

2.2.1 Fluvoxamine

Bánk[45] compared fluvoxamine 25 mg/day and amitriptyline 25 mg/day as prophylactic compounds in a double-blind and randomized study in 70 patients with migraine, with and without aura. After a run-in period of 4 weeks, 32 patients were treated with either drug for 3 months. Significant improvements on a proprietary headache index were observed in both groups, with significantly more adverse effects and a higher withdrawal rate in the amitriptyline group. The lack of a placebo group and the relatively low dose of amitriptyline reduce the clinical value of this study.

2.2.2 Citalopram

Rampello et al.[53] investigated the prophylactic effect of citalopram (20 mg at bedtime) versus amitriptyline (50 mg at bedtime) for 4 months (after a run-in period of 3 months) in patients with migraine (n = 44) and tension-type headache (n = 44) according to the International Classification of Headache Disorders (ICHD)-2 criteria[1] and concomitant depression according to the Diagnostic and Statistical Manual of Mental Disorders – 4th Edition (DSM-IV)[71] criteria in an open randomized trial. Patients who did not improve by at least 30% after these 4 months were subsequently treated with a combination of both drugs for a further 4 months. Primary endpoints (attack frequency, number of headache days and Hamilton Depression Rating Scale scores) significantly improved after 4 months in both groups. Headache endpoints improved more in the amitriptyline group; however, adverse effects were higher in this group as well.

2.2.3 Sertraline

In a small, double-blind study by Landy et al.,[72] 27 patients with migraine according to the ICHD criteria received sertraline (50–100 mg) daily or placebo for 2 months. No significant improvement on proprietary impairment and headache indices was observed. The withdrawal rate was high at 11 of 27 patients.

2.2.4 Paroxetine

Only two case reports suggest an efficacy for paroxetine, in a total of four patients,[73,74] so that no sound evaluation is possible.

2.2.5 Femoxetine

Because sale of femoxetine has been discontinued, we have not further evaluated the results of two small placebo-controlled trials.[75,76]

2.2.6 Fluoxetine

Fluoxetine is certainly the most extensively studied SSRI in migraine prevention. Migraine has been associated with dishabituation to external stimuli.[77] Ozkul and Bozlar[78] showed that a loss of habituation of visual evoked potentials in migraine patients normalized on fluoxetine 20 mg/day. In addition, migraine attack frequency diminished significantly. In a prospective study by Krymchantowski et al.[52] in 49 patients with transformed migraine, amitriptyline 40 mg was found to be equally effective as a combination of amitriptyline and fluoxetine (40 mg/day), which argues against a strong efficacy of fluoxetine. In another small (n = 15) open-label study, Oguzhanoglu and co-workers[79] compared the efficacy of fluoxetine 20 mg/day and

amitriptyline 50 mg/day in migraine patients on headache days, pain severity and duration. Only pain duration in the fluoxetine group improved significantly within 3 months.

Saper and co-workers[80] could not find a significant effect of fluoxetine 20–40 mg daily compared with placebo after 3 months of intake on headache self-assessment scales, a proprietary headache index or number of severe headache days per week. In another double-blind placebo-controlled study,[81] a significant improvement on a proprietary headache index was seen, but the withdrawal rate was high, the overall number in each group was low (n = 8), and the results were not corrected for multiple testing. Thus, the results should be interpreted with caution. The same holds true for another study by d'Amato and colleagues[82] who found a significant improvement on a proprietary headache index in those receiving fluoxetine 20 mg/day compared with placebo. This finding is limited by several shortcomings: only longitudinal analyses were carried out in each group, the placebo group was much smaller than the verum group, and no withdrawals were reported. No depressed patients took part in this study. The enantiomer, S-fluoxetine, showed promising results in a placebo-controlled, double-blind, randomized study, leading to a significant decrease of attack frequency, although the withdrawal rate was high[83] (see table VI for further details of placebo-controlled studies).

In conclusion, current data on the use of SSRIs in migraine prevention favours the use of fluoxetine. However, it should be considered that these studies are partly inconsistent and small in number of patients. A recent Cochrane review revealed that beneficial effects from SSRIs are equivalent to those of the placebo group within 2 months of therapy.[61] Thus, SSRIs have not yet shown an efficacy comparable to that of amitriptyline, but can be considered in patients with contraindications for tricyclic antidepressants or who have discontinued tricyclics as a result of

Table VI. Double-blind randomized placebo-controlled studies on fluoxetine in migraine

Study	N[a]	Design	Run-in	Drugs compared (daily dose)	Duration (mo)	Efficacy parameter	Results
Saper et al.[80] (1994)	58 (44)	mc, pg	4 wk placebo	Fluoxetine 20–40 mg, placebo	3	Proprietary headache index, number of headache-free days/wk and days/wk with severe headache; visual analogue scales for: overall headache status, frequency, average intensity, mood and energy level; BDI	No effect on any pain parameter; only mood improvement by the end of the last month without changes in the BDI
Adly et al.[81] (1992)	32 (18)	pg	2 wk	Fluoxetine 20 mg every 2nd day up to 40 mg/day, placebo	2	Proprietary headache index (daily score based upon headache diary, subjective intensity and amount of abortive medication); Zung depression rating scale	Decrease in headache score after 4 weeks in fluoxetine group, no change in placebo group; Zung scores unchanged
d'Amato et al.[82] (1999)	52 (52)	pg	4 wk	Fluoxetine 20 mg/day, placebo	6	Total pain index (based upon pain intensity and hours of headache/mo)	Significant reduction of total pain index in fluoxetine group only
Steiner et al.[83] (1998)	53 (33)	mc, pg	4 wk placebo	S-fluoxetine 40 mg (=80 mg racemic fluoxetine), placebo	3	Primary: attack frequency per mo; secondary: migraine days/mo, severity of each attack, amount of abortive medication, PGIDS	Significant reduction of attack frequency in mo 2 and 4 in the verum group; no significant changes in secondary efficacy measures except variables of PGIDS in mo 3 and 4

a Number of patients included (number of patients evaluated). Severe psychiatric illness was an exclusion criterion in the first study.

BDI = Beck depression inventory; **mc** = multicentre; **pg** = parallel groups; **PGIDS** = patient global impression of disease severity.

adverse effects. Although current data are most convincing for fluoxetine, in combination therapy we would generally recommend citalopram or escitalopram because of their relatively low interaction potential. One should be aware that SSRIs have been associated with new-onset or exacerbation of pre-existing headaches as an adverse effect.[84-86]

2.3 Noradrenergic and Specific Serotonergic Antidepressants

2.3.1 Mirtazapine

Low doses of mirtazapine (at least 7.5 mg at bedtime) improved migraine relapses in single patients, but controlled studies are lacking.[87,88] At this dose, mirtazapine is also a suitable sleep-inducing agent. The mechanism of action could be explained by its blockade of presynaptic α_2-receptors, which especially increases noradrenaline or dopamine synaptic availability. Moreover, mirtazapine blocks postsynaptic 5-HT_2 and $5HT_3$ receptors, which may be responsible for the effect in headache.[89] Usual adverse events are sedation (possibly positive), weight gain, dry mouth or drowsiness. In rare cases blood dyscrasias may occur. The interaction potential of mirtazapine appears to be low and therefore the drug may be especially helpful if the patient requires further co-medication.[43,90] However, some low inhibitory effects of mirtazapine on CYP2D6, CYP1A2 or CYP3A4, although with minor clinical relevance, should be taken into consideration.

2.3.2 Mianserin

The 5-HT_2 receptor antagonist mianserin has been tested in two randomized, placebo-controlled, double-blind studies. Monro et al.[91] examined 38 migraine patients receiving mianserin 60 mg/day after a placebo run-in period of 2 weeks and subsequent drug intake for 4 months. They showed a significant reduction of headache frequency and a proprietary headache index after 1–3 months, whereas no significant results could be seen after the fourth month. Beck Depression Inventory (BDI) ratings did not change. In another small crossover study (n = 20) migraine patients received placebo, clonidine 15 mg and lastly mianserin 30 mg for 90 days each, with a washout period of 1 week between each drug.[92] With mianserin, the attack frequency increased significantly within the first month, while it decreased significantly within the following 2 months. Effects on migraine duration and intensity were not significant, while effects on depression and anxiety were ambiguous.

In conclusion, we do not feel that current data are sufficient to promote widespread use of mianserin in migraine treatment.

2.4 Serotonin-Noradrenaline (Norepinephrine) Reuptake Inhibitors

2.4.1 Nefazodone

In an open-label study in 48 patients with migraine, nefazodone was effective in preventing migraine attacks at a median daily dose of 300 mg. Some 75% of the participants showed a marked reduction of headaches of at least 50%.[93] The overall enhanced sedation effect at bedtime may be an advantage. The drug was well tolerated by migraine patients and is possibly suited in other chronic headaches, such as chronic tension-type headache. Tiredness, occasionally nausea, hypotonia, blurred vision or weight gain occurred.[90]

Nefazodone is an inhibitor of CYP3A4 and so the compound is prone to show clinically relevant interactions. The concentrations of the anxiolytic buspirone rose by a factor 20, the levels of nefazodone itself increasing only slightly;[90,94] therefore, low buspirone doses of 2.5 mg/day may be sufficient in combination with nefazodone. Coadministration of carbamazepine decreased plasma nefazodone concentrations by 90%, while carbamazepine levels increased by 23%. After concomitant treatment with nefazodone, up to 30% higher levels of digoxin were measured. Plasma levels increase 20-fold following coadministration of nefazodone and HMG-CoA reductase inhibitors such as simvastatin (a substrate of CYP3A4). The risk of drug interactions for pravastatin or fluvastatin, which are not substantially metabolized via CYP3A4, is obviously lower. As a result of the interaction profile of nefazodone, combinations with alprazolam,

triazolam and particularly terfenadine, astemizole, cisapride or pimozide should be avoided. Because of cases of severe hepatotoxicity,[95] the drug has been withdrawn from the market in many countries, although it is still available in the US.[96] Considering these potentially severe, albeit rare, adverse effects and the limited available data, the sense of prescribing this drug to nefazodone-naïve patients is debatable.

2.4.2 Duloxetine

Duloxetine has been promoted as being especially useful in painful somatoform and depressive disorders, although in a recent meta-analysis of duloxetine in depressed patients with pain, no effect on painful symptoms could be found.[97] In migraine, a retrospective analysis of 65 migraine patients receiving 30–60 mg daily for at least 2 months revealed a significant reduction in attacks per month. Interestingly, those with a co-morbid depression did not benefit significantly in a subgroup analysis, while those with a co-morbid anxiety disorder had a greater benefit than all 65 migraine patients together.[98] A recent open-label trial (n = 30) examined the effects of duloxetine 60 mg/day for 2 months[99] in patients with major depression according to the DSM-IV criteria and a concurrent chronic migraine or chronic tension-type headache. Mean visual analogue scale scores and the number of headache days per week decreased significantly, as did depression scores. As for other drugs, current data are promising, but well designed prospective studies are needed to further evaluate the therapeutic potential in migraine prevention.

2.4.3 Milnacipran

Milnacipran has not been examined in headache therapy.

2.4.4 Venlafaxine

There have been four studies of venlafaxine in migraine. In one open-label study (n = 42), migraine patients received venlafaxine 18.75–37.5 mg daily for 2–4 months, which caused a reduction in headache attacks by at least 50% in 88% of the participants.[100] This overwhelming effect at very low doses calls for a critical evaluation. In another retrospective study (n = 114), venlafaxine extended release was given to migraine patients in a median dosage of 150 mg/day. After 6 months, the number of headache days decreased significantly. The results in patients with a concomitant depression did not differ from those without depression. These positive results are limited by the retrospective design, the fact that concomitant migraine prophylactics were allowed, and that the majority of patients had simultaneous tension-type headache.[101]

In a randomized, double-blind, crossover trial (n = 52), patients with migraine with and without aura received venlafaxine extended release 150 mg/day or amitriptyline 75 mg/day extended release for 3 months each, with a washout phase of 1 month. The number of attacks per month as well as the duration and intensity of the attacks decreased significantly with both drugs.[102] More adverse effects and withdrawals occurred during treatment with amitriptyline. In a recent placebo-controlled, double-blind, randomized study (n = 60), venlafaxine extended release 75 or 150 mg daily was administered. Patients receiving venlafaxine 150 mg had significantly less headache days than placebo, and patients on either dosage of venlafaxine had a significantly decreased consumption of analgesics and a higher level of patient satisfaction.[103] Adverse effects occurred more often with venlafaxine, but remitted quicker than in the placebo group. However, the impact of this is limited by the low number of patients in each group (n = 15–17).

It should be kept in mind that serotonin syndrome has been described when switching patients from monoamine oxidase inhibitors (MAOIs) to venlafaxine.[104] Typical adverse effects of venlafaxine are nausea, vomiting, constipation, sedation or dry mouth, and reports about discontinuation syndromes. Metabolism via the CYP2D6 isoenzyme disposes venlafaxine to corresponding interactions, although no clinically relevant interactions have been reported.[90,105] However, concomitant use of almotriptan or frovatriptan can theoretically lead to adverse effects, as both are metabolized via CYP2D6.[106]

In conclusion, current data support the use of venlafaxine in migraine prevention, especially in those patients with contraindications to amitriptyline and those with intolerable adverse effects with amitriptyline.

2.5 Monoamine Oxidase Inhibitors

First reports about the efficacy of MAOIs date back to 1969, when Anthony and Lance[107] yielded a good therapeutic result in refractory migraine patients with the nonspecific MAOI phenelzine in an open-label study. This positive result was reproduced by others later.[4] However, the potential adverse effects, the special diet and the various interactions restricted the use this drug to refractory patients.

2.5.1 Tranylcypromine

Tranylcypromine is a nonspecific and irreversible MAOI used in the treatment of depression. There are no studies in migraine patients meeting current quality standards, and adverse effects and interactions are unfavourable. In addition, the compound can provoke headache itself.[108]

2.5.2 Moclobemide

The reversible inhibitor of MAO-A (RIMA) moclobemide is better tolerated and thus is currently preferred to nonspecific MAOIs. In a retrospective analysis in 42 patients with migraine according to the ICHD criteria, moclobemide 300–450 mg daily given for an average of 8 months led to an improvement in 35 of 42 patients, i.e. approximately 83% based on pain intensity, headache days per month and severity of accompanying symptoms.[109,110] Seven of 42 (16%) patients discontinued MAOI treatment as a result of adverse effects. Although impressive, these results have to be interpreted with caution, as some patients took concomitant medication with other migraine-preventing drugs and some patients experienced an additional tension-type headache.

Various drugs showing efficacy in retrospective or open-label studies have failed to reproduce this effect in controlled, double-blind, prospective studies.[111] With the triptans, potentially dangerous interactions were found between moclobemide and sumatriptan as well as rizatriptan.[112-114] Unlike sumatriptan and rizatriptan, some of the newer triptans should not interact with moclobemide at all,[104] e.g. frovatriptan,[115] or at a much lower degree and without clinical adverse effects, e.g. almotriptan[116] or zolmitriptan.[117] Combinations of a MAOI such as phenelzine with a β-adrenergic receptor antagonist (β-blocker) may improve the tolerability of either drug, but should be used only in special cases, as when an interaction with nutritional ingredients ('cheese syndrome') cannot be anticipated.[118] Therefore, a combination of moclobemide and triptans cannot generally be recommended.

2.6 Noradrenaline and Dopamine Reuptake Inhibitors

2.6.1 Bupropion

Controlled studies on the efficacy of bupropion in migraine prevention are not available. In a single case report, a dramatic improvement in depression and migraine frequency and severity was reported.[119] In a case series of nine patients with chronic daily headache, seven had fewer headaches.[120] On the basis of current data, there is insufficient evidence for the use of bupropion in migraine prevention. It should be kept in mind that up to 26% of patients receiving bupropion experience headache as an adverse effect. As the compound does not influence the serotonin system and the role of dopamine in migraine pathophysiology remains ambiguous,[121] it may not be efficacious in controlled studies.[122]

2.7 Occasionally Used Antidepressants in Clinical Practice

2.7.1 Opipramol

Only one randomized, double-blind, placebo-controlled study (n = 59) has shown beneficial effects of opipramol on migraine.[123] Treatment with opipramol 150 mg/day for 12 weeks after a run-in phase of 6 weeks led to a significant reduction of migraine attacks in 33% of patients after 6 weeks and 49% after 12 weeks. However, these promising results have to be regarded with caution as only a few patients in the verum

(n = 14) and the placebo groups (n = 13) were eligible for final analysis because of the high withdrawal rate. In addition, inclusion criteria were vague.

2.7.2 Trazodone

In paediatric migraine, the triazolopyridine derivative trazodone (5-HT_2 receptor antagonist and serotonin reuptake inhibitor) was not unequivocally effective. In a study with 40 patients aged 7 to 18 years experiencing migraine, the effects of either trazodone (1 mg/kg bodyweight per day) and placebo after intake of 3 months each was assessed in a randomized, double-blind, crossover study.[124] While both groups showed significant improvements (lower attack frequency and duration) in the first 3 months, only the placebo-trazodone group improved further in the 3 months following crossover. A Cochrane review on paediatric migraine concluded that trazodone was ineffective in reducing the number of migraine attacks.[57]

In adults, one report suggests an effect of trazodone in migraine.[125] However, multiple interactions limit its use, particularly in the elderly,[89,126] whereas its sleep-aiding effect may be a welcome side effect. The main metabolite of trazodone, m-chlorophenylpiperazine, can cause migraine-like headache.[113]

In conclusion, no sound data on efficacy of trazodone in migraine prevention in adults are available.

2.7.3 Other Drugs

There is currently no evidence for efficacy of the SNRIs reboxetine and maprotiline in migraine prevention. Tianeptine, a selective serotonin reuptake enhancer, was effective in depression but has not been investigated in migraine patients.[127]

3. Risk of Severe Pharmacodynamic Interactions

It is beyond the scope of this review to summarize and assess all possible phase I (mixed-function oxidases) or phase II (e.g. uridine diphosphate glucuronosyl transferases) interactions associated with therapy of migraine.[106,128] All antidepressants are metabolized via the CYP isoenzyme system in the liver. At the same time, they affect the metabolism of other drugs, including other antidepressants. Major interactions are given in the reference by Spina et al.[129] While fluoxetine, fluvoxamine, paroxetine and sertraline are strong inhibitors, citalopram, escitalopram, venlafaxine, reboxetine and mirtazapine are relatively weak inhibitors of the CYP system and have a lesser risk of drug interactions.[129]

The most important clinical interaction when serotonin release enhancing or reuptake inhibitors are combined is the serotonin syndrome, which must be considered when hyperactivity, confusion, hyperreflexia, hyperpyrexia, tachycardia, myoclonus, ocular oscillations or tremor are seen. A well known but possibly critical combination in this regard would be the combination of an SSRI and a MAOI. In general, all drugs inhibiting reuptake of serotonin can provoke serotonin syndromes. Theoretically, adding triptans to a serotonergic drug (especially SSRIs and SNRIs) could increase this risk even more, in addition to an increase in other adverse effects. This led the US FDA to release a warning in 2005 that the risk of a serotonin syndrome increases if SSRIs or SNRIs are combined with triptans.[130] An even higher risk could be assumed if further serotonergic drugs were added to this combination. However, this warning has been subject to discussion among headache specialists. Evans[131] reviewed all 27 cases analysed by the FDA as the basis for their warning plus two additional cases not included in the analysis. Only 7 of all 29 cases met the criteria of serotonin syndrome proposed by Sternbach,[132] and none met the Hunter serotonin toxicity criteria.[133] In addition, other studies did not suggest increased rates of serotonin syndrome.[131,134] Thus, the prescribing physician should be well aware of the potential risks associated with serotonergic drugs, but should not withhold effective therapies from patients with migraine and concomitant psychiatric disease.

Theoretically, sumatriptan and rizatriptan (MAO-A metabolism) could particularly interact with MAOIs or other mainly serotonergic drugs. Almotriptan or zolmitriptan (MAO and

cytochrome metabolism) should have fewer interactions with serotonergic drugs and RIMAs.[104] Eletriptan or naratriptan (only P450 metabolism) should not cause any interaction. However, in clinical practice even subcutaneously administered sumatriptan seems to have little interaction with concomitant drugs and a low rate of psychological adverse effects,[135] although adverse effects are known to be highest with this formulation.[136] The same holds true for the interaction between moclobemide and qalmotriptan, which did not cause substantial adverse effects, although the almotriptan concentration increased by some 37%.[137] In general, we would recommend oral or nasal preparations because of the lower risk of adverse effects.

When changing from one antidepressant to another, a delayed intake of the new drug related to the half-life of the former drug seems reasonable, e.g. up to 5 weeks after intake of fluoxetine before switching to MAOIs. Patients should be advised to seek medical advice should symptoms suspicious of serotonin syndrome occur. Treatment with any serotonergic substance should be instantly interrupted. In severe serotonin syndrome, intensive care treatment with dantrolene infusions, benzodiazepines or serotonin antagonists such as cyproheptadine or methysergide may be helpful.[138,139] Simultaneous intake of more than one serotonergic drug should be performed with caution, and only in compliant patients who have been briefed to seek medical help if adverse effects occur. We would recommend particular care when MAOIs and triptans are given together, as well as when combinations of more than two serotonergic drugs are given. In cases of polypharmacy, the patient should be informed about potentially severe adverse effects, and plasma concentrations of drugs such as lithium, digoxin, phenytoin, valproate and carbamazepine should be checked regularly as well as the serum concentrations of the antidepressants themselves. In addition, regular laboratory tests (especially blood count, liver and renal function tests) should be carried out routinely.

Clinicians have increasingly become aware of the potential prolongation of the QT interval with the use of antidepressants and antipsychotics,[140] which is especially important with patients receiving combinations of different drugs. The web-based 'International Registry for Drug-Induced Arrhythmias'[140,141] is a frequently updated registry of drug-induced arrhythmias. It is wise to regularly record an ECG during treatment with antidepressants, particularly tricyclic compounds. Special caution should be taken if these agents are not being used in regular doses, in patients with congenital long QT or Brugada syndrome or electrolyte disturbances, and in patients receiving additional drugs causing QT interval prolongation or that interfere with metabolic pathways of antidepressants.[142]

4. Clinical Appraisal

Antidepressants are second- or third-line prophylactic agents in patients with migraine alone. Antidepressants in migraine are likely to be considered only if other drugs (β-blockers, flunarizine, valproate and topiramate) have not reduced the number of monthly attacks or if concomitant depression (or other psychiatric disease) exists.

Controlled clinical trials substantiate the role of amitriptyline in this respect and venlafaxine represents a promising alternative. Although modern antidepressants such as mirtazapine or SSRIs showed positive results on migraine in various observational studies, a final assessment is not yet possible. The use of moclobemide has to be regarded with caution, as controlled clinical trials are lacking and the potential risk of serotonin syndrome needs to be considered. The future role of other modern antidepressants in migraine prevention, such as bupropion, is currently ambiguous. Pharmacotherapy of depression and migraine can be chosen from a broad range of drugs (tables III and VII), which enables the physician to take into account individual circumstances and provide a 'tailor-made' therapy.

The drug of first choice should be amitriptyline monotherapy. Further steps should be guided by the treatment response of migraine and depression. If migraine improves but depression requires an escalation of antidepressant therapy,

Table VII. Summary of drugs used in migraine treatment and prophylaxis according to recent the European guidelines[5]

Classes of drugs	Major mechanism of action
Acute treatment	
NSAIDs	COX inhibition (arachidonic acid metabolism)
Triptans	Serotonin 5-$HT_{1B}/_{1D}$-receptor agonists
Ergot alkaloids	Partial α-adrenergic/serotonin receptor agonism
Prophylactic treatment	
β-Blockers	β-Receptor-1 antagonism
Flunarizine	Calcium channel antagonism (histamine, dopamine, serotonin antagonism)
Valproic acid	Inhibition of voltage sensitive sodium/calcium channels via GABA mediation
Topiramate	Sodium channel antagonism, enhanced GABA inhibition, reduced glutamate excitation
Amitriptyline	Noradrenaline and serotonin reuptake inhibitor
Methysergide	Serotonin receptor antagonism
Gabapentin	Inhibition of voltage-sensitive sodium channels, binding to L-amino acids (glutamate)
Estrogen[a]	Selective estrogen receptor modulation, increase of serotonin receptors
Magnesium	Inhibition of acetylcholine release, calcium channel antagonism
Pizotifen	Serotonin receptor antagonism
Acetylsalicylic acid	Irreversible inactivation of COX-1 and -2 enzymes

a Not mentioned in the guidelines.

COX = cyclo-oxygenase.

augmentation with newer antidepressants, such as SSRIs, SNRIs or mirtazapine, can be helpful. Because of the low interaction, we prefer a combination with citalopram or escitalopram.[143] If depression improves and therapeutic escalation is required for migraine, we recommend a combination with a drug of first choice in migraine prevention. As flunarizine is contraindicated in depression, we prefer valproate, metoprolol (alternatively propranolol or bisoprolol) or topiramate.[5]

It should be kept in mind that depression as an adverse effect has been reported in up to 10% of epilepsy patients receiving topiramate.[144] However, other studies have found topiramate helpful in the treatment of depression.[145] The combination of topiramate and amitriptyline was equally effective in reduction of migraine frequency, duration and severity compared with either substance alone in a recent double-blind, randomized, controlled trial (n = 73), while depression scores improved more in the combination group. Interestingly, adverse effects were lowest in the combination group.[146]

Alternatively, β-blockers or other substances with a lower interaction potential, such as gabapentin, can be considered. Although depression as an adverse effect has been reported in several studies on β-blockers,[147] this issue is subject to discussion as some studies did not find increased rates of depression in patients receiving β-blockers, and pindolol has even been associated with beneficial effects as adjunctive treatment in depression.[148] Flunarizine, which is recommended in Europe, should be avoided, as it can lead to an aggravation of depression.[149]

Some patients may require a combination of antidepressants, which poses the risk of serotonin syndrome, especially if triptans are administered. However, the incidence of serotonin syndrome in these patients seems to be lower than would be expected.[131] In clinical practice, oral triptans are mostly well tolerated in patients receiving antidepressants, although we would recommend selection of triptans according to their metabolic pathways.[106] As almotriptan, zolmitriptan and naratriptan are metabolized via three or more different pathways,[106,150] they should be preferred in combination therapy with serotonergic antidepressants. In combination with other nonserotonergic drugs, sumatriptan and rizatriptan may be better choices as they are predominantly metabolized via the MAO system and do not interact with the CYP isoenzyme system to a relevant extent. More detailed information on metabolic pathways of the triptans are given in the article by Ferrari et al.[106]

Additional antiemetics, such as metoclopramide, domperidone (mainly in Europe), antipsychotics (mainly in the US) and dimenhydrinate should be selected individually. Domperidone and antipsychotics can cause QT interval prolongation (Center for Education and Research and Therapeutics),[139] and all of them can cause CNS adverse effects in combination with antidepressants.

As migraine occurs mainly in young and middle-aged women, weight gain is an important issue, as all antidepressants can cause weight gain.[151] Tricyclics and mirtazapine generally cause more weight gain than SSRIs and the newer antidepressants. In these situations, a combination with topiramate can be helpful, as it frequently causes weight loss.[152]

Our cautious recommendations for the use of antidepressants reflect the current lack of data on most substances. Specifically, more randomized, double-blind, placebo-controlled studies adhering to current quality standards such as the CONSORT (CONsolidated Standards of Reporting Trials) criteria[153] are needed to better evaluate the therapeutic potential of newer antidepressants. In addition, some of the older studies in particular did not diagnose migraine according to clear-cut diagnostic criteria (see table I). Another shortcoming in the presented studies is that a primary endpoint was not defined and a headache index had been used as the main efficacy measure. According to the International Headache Society Clinical Trials Subcommittee, the number of attacks per month should be used as the primary outcome variable.[154] Another heterogeneity is the fact that some of the presented studies examined migraine preventive efficacy only in those patients without a concomitant depression, while others allowed concurrent depression. Today, some guidelines adopt a rather strict approach recommending only amitriptyline,[5] whereas others, such as the US Academy of Neurology, recommend more drugs, albeit stressing the low quality of evidence in the corresponding drugs.[155]

Various herbal remedies have become increasingly popular, such as St John's wort (*Hypericum perforatum*) in depression and butterbur root (*Petasites hybridus*) and feverfew (*Tanacetum parthenium*) in migraine.[157,158] As these are over-the-counter drugs and regarded as 'natural' remedies by many patients, one should be aware that many patients are unlikely report use of these drugs on their own initiative. Indeed, in an Italian migraine clinic, 61% of patients did not inform their doctors about the use of complimentary and alternative remedies.[159] St John's wort can increase the risks of adverse effects or serotonin syndrome if taken together with an antidepressant.[160] In addition, some herbal remedies such as a kava (*Piper methysticum*) and butterbur root have been associated with hepatotoxicity.[161,162] Therefore, it is essential to ask the patient about the consumption of complementary and alternative therapies.

In order to minimize the consumption of drugs, the physician should consider advising regular aerobic physical exercise to patients, although current data do not allow a final judgement on its efficacy in migraine prevention.[163] In addition, behavioural therapies such as relaxation training, biofeedback and cognitive-behavioural training are moderately effective, and are recommended by the American Academy of Neurology and the German Neurological Society, although the body of evidence is weak as a result of the limited number of studies.[156,164] Beneficial effects for adjunctive treatment have been found in depression as well.[165]

As co-morbidity of migraine and depression includes bipolar II patients, the physician should be aware that use of antidepressants in those subjects can cause increased activation, induction of mixed states, increased cycling and hypomanic or manic switches.[166] In these patients, the physician should critically evaluate whether an antidepressant is still needed and valproate should be added (or given alone) as a mood stabilizer with proven antimigraine efficacy.[167]

5. Conclusions

In conclusion, the effective treatment of migraine in depressed patients calls for a specialized physician with neurological and psychiatric expertise and profound pharmacological knowledge, as complications and interactions can be numerous and potentially severe. Amitriptyline is certainly the drug of choice and venlafaxine shows promising results. However, more substantial studies adhering to the CONSORT criteria are needed to fully evaluate the therapeutic potential of antidepressants in migraine. The effective treatment of both disorders is essential, as one disease influences the other and

can therefore complicate treatment of both, although the ideal drug treating both disorders reliably is yet to be developed.

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